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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,790	10/01/2003	Christopher S. Piddington	99-10C1	2402

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EXAMINER	
ZOLTAN JONES, ALEXANDRA	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,790	PIDDINGTON ET AL.	
	Examiner	Art Unit	
	Alexandra Zoltan-Jones, PhD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/01/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-27 are rejected under 35 U.S.C. 101 because the claims are drawn to an invention that has no apparent or disclosed specific and substantial credible utility or a well established utility.

The instant application provides a description of an isolated polynucleotide encoding a polypeptide, and variants encoded thereby. The specification fails to teach a specific biological role for the claimed protein, or to identify a specific disease, disorder or physiological process in which the claimed subject matter would play a definitive role. Neither the specification not the prior art of record suggest any activity that the skilled artisan would consider to be well established. Because the claimed invention is not supported by a specific, asserted utility, credibility cannot be assessed.

The instant application discloses polynucleotide encoding zacrp5 (SEQID NO: 2) that the specification suggests, due to similarity to known DNA, belongs to the adipocyte complement related protein family, a family of proteins that plays a role in cell-cell and cell-extracellular matrix interactions (p2). Following complete characterization, this DNA and encoded protein may be found to have specific and substantial credible utility. However, such further characterization is part of the act of invention and until it has been undertaken, the claimed invention is incomplete. The instant situation is directly

analogous to Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound that was structurally analogous to other compounds that were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of any evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35USC 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility","[u]nless and until a process is refined and developed to this point- where specific benefit exists in currently available form- there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a parent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to the polynucleotides encoding zacrp5 polypeptides with an undetermined function or biological significance. One of skill in the art would appreciate from the instant application that the proteins described share a structural homology and modest sequence similarity to members of the adipocyte complement related protein family, who have known function in cell-ECM interactions. For example, zacrp5 is 48 percent identical with the whole molecule of zsig37, and is 57.4 percent identical with the C1q domain of zsig37 (Table 1A and 1B).

In the absence of knowledge of the biological significance of the specific zacrp5 polynucleotides, there appears to be no immediately obvious patentable utility for the

claimed polynucleotides. The specification contains several general assertions of utility for the polynucleotides and polypeptides of the claimed invention, but fails to establish any specific use for the nucleotides or polypeptides. The general assertions and reasons for lack of utility are discussed in detail below.

The specification teaches that the nucleic acids are useful as probes or primers. One asserted utility is that the zacrp5 gene, a probe comprising zacrp5 DNA or RNA, or a subsequence thereof can be used to determine if the zacrp5 gene is present on chromosome 16 or if a mutation has occurred (p82). This asserted utility is credible and specific, but it is not substantial. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the nucleic acid probes to identify such. The specification also asserts that the probes can be used to detect tissues expressing SEQID NO: 2; however the significance of any tissue specific pattern of expression is not disclosed, nor is any pattern of SEQ ID NO: 2 tissue expression. Therefore, this asserted utility is not specific and is not substantial.

The specification asserts that SEQID NO: 2 has Acrp30 and zsig37-like biological activity, such as modulation of cell-cell or cell-ECM interaction, based on its structural similarity to Acrp30 and zsig37, and other members of this protein family. However, the art indicates that although these family members share structural similarity, they are likely functionally diverse. For example, zsig37 is predominantly expressed in heart, aorta and placenta; has an effect on TF-1 cell adhesion; enhances growth of A7-BaF-3 cells; slightly inhibits DA-1 cell growth, and appears to increase serum free fatty acid levels (WO 99/004000, A4 on IDS and US Patent 6,265,544 B, A1 on IDS). The zsig39

protein is expressed in heart and small intestine and, opposite of zsig37 action, appears to lower serum free fatty acid levels (US Patent 6,482,612 B1, A2 on IDS). Acrp30 is expressed exclusively in adipocytes, and appears to be secreted from adipocytes in response to insulin exposure (US Patent 5,869,330, A3 on IDS). Thus, it is clear from the art that structural similarity between Acrp30, zsig37 and zsig39 does not predict expression pattern or functional similarity. Therefore, the assertion in the specification that SEQID NO: 2 has activities similar to other polypeptides in this family is not considered a substantial assertion of utility, as significant further research would be required of the skilled artisan to determine what those activities are.

Furthermore, generally the art acknowledges that function cannot be predicted solely on the basis of structural similarity to a protein found in the sequence database. Consistent with the state of the art, Skolnick et al (2000, Trends in Biotech. 18:34-39. A14 of IDS) warns about the shortcomings of sequence based methods for protein function prediction due to the "multifunctional nature of proteins," further stating that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (p36). Similarly, Bork et al states that the error rate of functional annotations in the sequence database is considerable, making it increasingly difficult to infer correct function from a structural comparison of a new sequence with a sequence database (Bork et al. 2000, Genome Research 10: 398-400, A15 on IDS). Doerks et al. (1998, Trends in Genomics 14: 248-250, A16 on IDS) agree that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in

underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with a functional similarity. Smith et al (1997, Nature Biotechnology 15:1222-1223, A17 on IDS) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Finally, Bork et al. (1996, Trends in Genetics 12:425-427, A19 on IDS) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of an already known protein. Such questionable interpretations are written in to the sequence database and are then considered facts.

The specification asserts that the claimed polynucleotide can be used in diagnosing genetic disease. The specification does not disclose a nexus between any genetic disease and altered levels or forms of polynucleotides encoding the polypeptide of SEQID NO: 2. Significant further experimentation would be required of the skilled artisan to determine such a nexus.

The specification asserts that the gene encoding SEQID NO: 2 is located on chromosome 16, and teaches use of a probe comprising zacrp5 DNA or RNA as a probe to determine if the zacrp5 gene is present on chromosome 16 or if a mutation has occurs (p82). However, the chromosomal location of the gene was never precisely mapped. In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed as well as the significance of the location. Substantial further research would be required of the skilled artisan to determine where on

chromosome 16 this particular sequence is mapped in order to use the nucleic acid molecule in the asserted utility as a chromosomal map probe.

The specification asserts that the claimed polynucleotide or encoded polypeptide can be used to treat a variety of autoimmune, tissue remodeling, infectious and cancerous diseases. Although the utility is specific and credible, it is not substantial. The specification fails to establish a nexus between the polynucleotides or polypeptides of the instant invention and any disease or pathological disorder. Significant further experimentation would be required of the skilled artisan to determine the nexus, and to subsequently determine how to administer SEQID NO: 2 for the desired therapeutic effect.

The specification asserts a use for the polypeptides in studying mammalian cellular metabolism; however, the specification has not disclosed a metabolic activity for SEQID NO: 2. Since significant further experimentation would be required of the skilled artisan to determine the effect, if any, of SEQID NO: 2 on metabolism, and then to determine how to administer SEQID NO: 2 or an antagonist thereof to the appropriate tissue in order to gain a therapeutic effect, this is not a patentable utility.

The specification teaches a use for the polypeptide to isolate other proteins to which it binds. Since the encoded polypeptide has no specific, substantial and credible utility, there is also no specific, substantial and credible utility for anything that specifically binds SEQID NO: 2 in the absence of any other disclosure regarding those entities.

Therefore, in the absence of a well-established utility, and in the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 USC 101.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Additionally, the specification is not enabling for polynucleotides encoding variants of SEQID NO: 2. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein sequence where such the amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. various sites or regions directly involved in binding, in activity and in providing the proper three-dimensional spatial orientation of binding and active sites. These or other regions may be critical determinants of

antigenicity. These regions can tolerate only relatively conservative substitutions, or no substitutions at all (Wells, 1990 Biochemistry 29:8509-8517, A20 on IDS; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, p492-495, A21 on IDS).

Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions of the protein which are tolerant to change (e.g. such as by amino acid substitution or deletion), and the nature and the extent of the changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, the sites may not be sufficient, as the ordinary artisan would immediately recognize an active or binding site must assume the proper three-dimensional configuration to be active, which is dependent upon surrounding residues. Thus, substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trend in Biotech 18(1): 34-39; Doerks et al., 1998, Trends in Genetics 14: 248-250; Smith et al., 1997, Nature Biotechnology 15: 1222-1223; Brenner, 1999, Trends in Genetics 15:132-133, A18 on IDS; Bork et al., 1996, Trends in Genetics 12:425-427, A19 on IDS). Due to the large quantity of experimentation necessary to

generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, and what specific activities SEQID NO: 2 has, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art, and the breath of the claims which fail to recite any structural or function limitations, undue experimentation would be required of the skilled artisan to make and/or use the invention in its full scope.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexandra Zoltan-Jones, PhD whose telephone number is (571) 272-3325. The examiner can normally be reached on Monday-Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AZJ

Lorraine Spector

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